

The Action of Anæsthetics on Living Tissues. Part I.—The Action on Isolated Nerve.

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Introduction.

The action of anæsthetics on isolated nerve has already been studied by Waller* as regards the effect on the negative variation in the sciatic of the frog, and by myself in mammalian nerves.† In the course of these researches it became evident that the anæsthetics used (chloroform, ether, carbon dioxide) affected not only the negative variation, but also the injury current, and as this action has not been studied before, as far as I am aware, it seemed desirable to investigate the matter not only in nerve, but also in other tissues.

The inquiry falls naturally under two heads: first, in how far the phenomena throw light on the processes of nerve action; and, secondly, as regards the chemical and physical action of anæsthetics on the animal protoplasm generally. These are obviously only parts of the same story, but for convenience I have considered the subject mainly under the first heading in this part, leaving the more general question to a future occasion.

Experiments.

If the sciatic nerve of a frog be taken and a fresh transverse section be made at the distal end, and this end be placed in contact with one non-

* Waller, "Lectures on Animal Electricity," 1897, and 'Proc. Physiol. Soc.,' November 13, 1897, etc.

† 'Roy. Soc. Proc.,' vol. 71, p. 264, and vol. 73, p. 166.

polarisable electrode, while another electrode rests on an uninjured longitudinal surface, the galvanometer will indicate a difference of potential which declines at a certain rate. This can be measured either by photographing the movement of the galvanometer spot, or, more accurately, by balancing against a known potential, reading the potentiometer at convenient intervals of time, and plotting the figures on squared paper; this latter method eliminates any change in the resistance of the object. The curve obtained is concave to the abscissæ, neglecting a variation which is occasionally found during the first five minutes of the experiment.

If, when this curve has assumed a typical form, CHCl_3 vapour be applied to the nerve, a sudden drop is observed. If the vapour is weak, this is followed by a recovery when the CHCl_3 is removed, if the vapour is strong (12 per cent. or over) the drop is permanent (fig. 1). This may be due

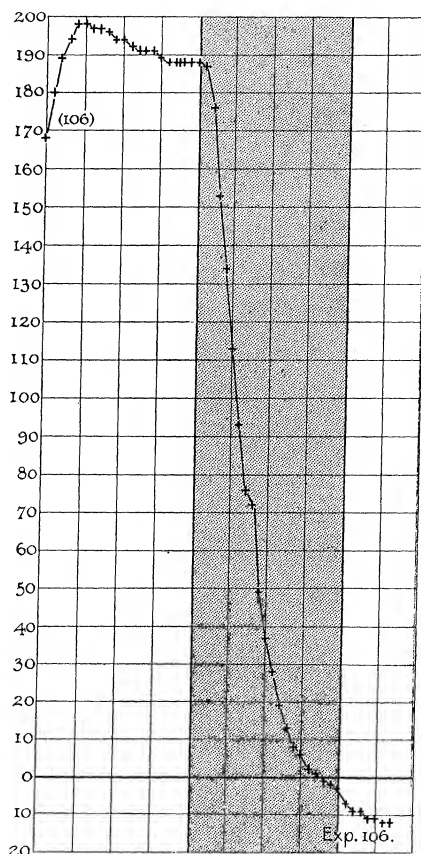


FIG. 1.—Sciatic of Frog. CHCl_3 vapour at 12.5 per cent. between the vertical bars.
Ordinates 1 mm. = 0.0001 volt. Abscissæ 1 mm. = 15 seconds.

to events occurring either at the cut end, or at the longitudinal surface or both, the experiments in Series II were undertaken to determine which of these factors predominated.

Series II.

The nerve-chamber was divided by a transverse gas-tight partition of modelling wax, so that the anæsthetic could be applied either to the cut end A or to the longitudinal surface B (fig. 2). The figures obtained from the

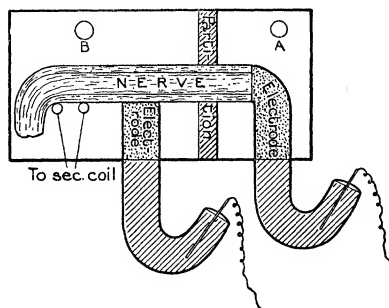


FIG. 2.—Nerve chamber.

potentiometer readings have been plotted out to a scale on the ordinate of which one division = 0·0001 volt, and on the abscissa one division = 15 seconds. The point at which the anæsthetic was applied was taken as the zero, and the relative heights plotted from this, the values are, therefore, relative and not absolute (fig. 3). The figures under the middle part of each curve indicate the percentage of CHCl_3 vapour, as measured by Waller's densimetric method.* The vapour was contained in a bag of gold-beaters' skin; the leakage from this was ascertained to be small during the time taken by an experiment of this kind. Here, as elsewhere in this paper, I have only considered experiments where the results are sufficiently concordant to admit of a consecutive series being employed without having to reject isolated experiments. Any unsuspected errors are, therefore, of a constant magnitude throughout a given series.

It will be seen that—

- (1) CHCl_3 to cut end of nerve causes an *increase* in the injury current.
- (2) This increase is roughly proportional to the strength of the CHCl_3 vapour up to about 12 per cent., greater concentration then gives no further increase.
- (3) CHCl_3 to longitudinal surface causes a decrease of the injury current.

* Waller and Geets, 'British Medical Journal,' June 20, 1903.

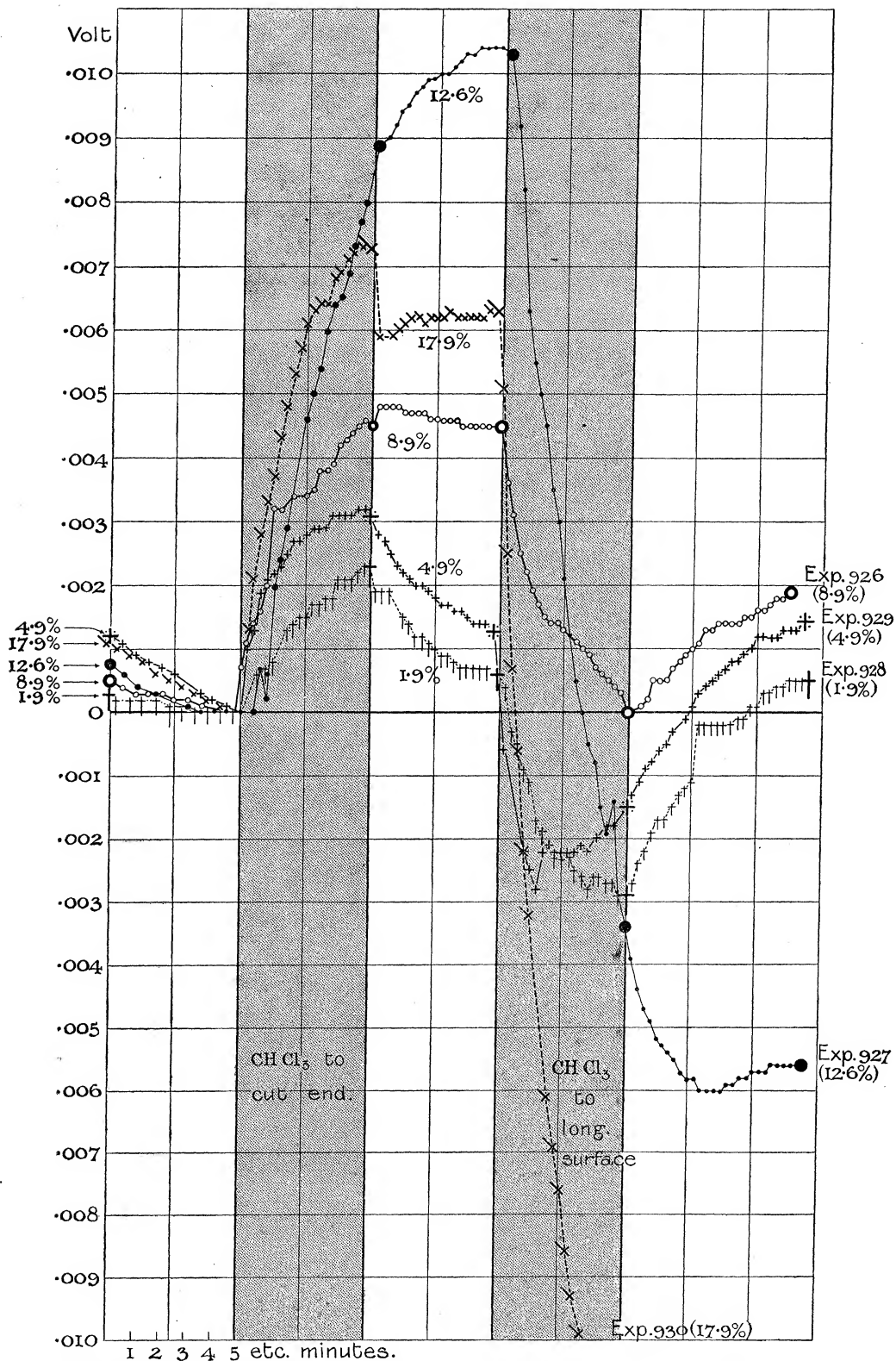


FIG. 3.—Series II. Relative increase and decrease of injury current by CHCl_3 vapour at different strengths. Ordinates 1 mm. = 0.0001 volt. Abscissæ 1 mm. = 15 seconds.

(4) Recovery takes place when the vapour is weak (9 per cent. or less), not occurring when the strength is 12 per cent. or more.

Series III.

The method adopted in Series II, while suitable for percentages of CHCl_3 from 1 to 10, is defective in many ways, and an apparatus was designed to deliver a constant high percentage of CHCl_3 , saturated with water vapour, and at a constant temperature. This consisted of a foot bellows with a branched delivery tube, one limb of which passes to seven Fresenius flasks, the first three containing CHCl_3 , the next water, the next two contain a mixture of CHCl_3 and water, and the last is empty. The apparatus delivers moist CHCl_3 vapour at a concentration of 13 to 17 per cent. (depending on the temperature of the first flask) with a variation in strength of about 0.5 per cent. and a temperature variation of about 0.4°C ., and by estimating the strength of the vapour after it has passed through the nerve-chamber, and noting the temperature before and after each experiment, these residual errors can be allowed for. The five flasks on the other limb of the air supply contain water, and a small stream of air passing through them serves to ventilate the other part of the nerve-chamber, thus guarding against accidental escape of CHCl_3 . A similar apparatus is used for ether: in this case the percentage is about 45. Unless otherwise stated, all further experiments were made with this apparatus, with occasional modifications.

In this series the strength of the CHCl_3 vapour was 12.5 (± 0.5 per cent.), and was applied for 10 minutes. The details of the various experiments differed. The values are now absolute, and have been corrected for electrode current. Each ordinate division = 0.002 volt; each abscissa division = 15 seconds.

In Experiments 108 and 107 (nerves of Frog A) the CHCl_3 was applied first to the longitudinal surface and then to the cut end. In Experiment 109 (Frog B) the same course was followed, only without making a fresh section, the curve therefore begins close to the zero line. In these three experiments the curves fall at first, the effects being naturally opposite in sign to those in the next three experiments—Nos. 111, 110, and 117—where the cut end is first affected. No. 110 is practically a repetition of Series I, No. 111 the same without a fresh section, and No. 117 shows the effect of ether applied for five minutes instead of ten.

Considering the first half of each experiment—

(1) CHCl_3 (Experiment 111) and ether (Experiment 117) to the distal end of a nerve cause a rise in potential, approximately equal in amount.

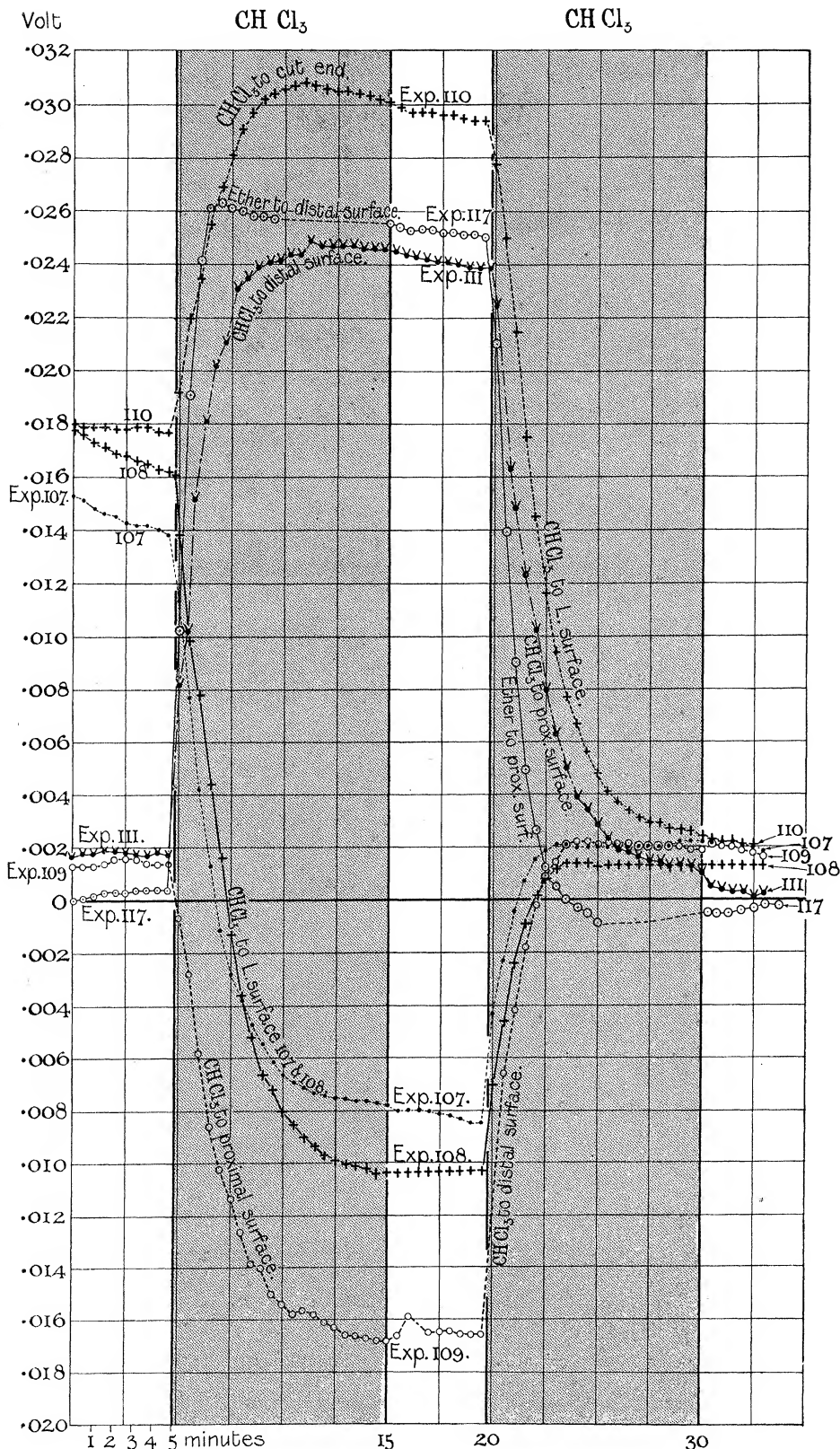


FIG. 4.—Series III. CHCl₃ of 12.5 per cent. and ether of 50 per cent. to either end of the nerve alternately. Ordinates 1 mm. = 0.0002 volt, abscissæ 1 mm. = 15 seconds. Expts. 107 and 108, CHCl₃ to L. surface and then cut end. Expt. 110, cut end and then L. surface. Expts. 109 and 111, CHCl₃ to different ends *without* a previous section. Expt. 117, ethers 50 per cent. to cut end and then L. surface.

(2) The effect of a previous section (110) is to produce a somewhat larger rise.

(3) CHCl_3 to the proximal end produces a fall in potential (107, 108, 109). When there is no previous section (109) the experiment is obviously identical with Experiment 111; when there is a previous section, the total effect is less. In other words, if

x = effect of section, and

y = effect of CHCl_3 in the first part of each experiment,

Exps. 109 and 111 = y ,

„ 107 „ 108 = $x - y$,

„ 110 = $x + y$.

These results are discussed subsequently in connection with the question as to whether x and y are due to the same mechanism in the nerve or not. Later experiments (Series V and VI) point to an affirmative answer; as regards this present series, it appears that y is of the same order of magnitude as x , whether CHCl_3 or ether is used, and that y has the same direction of current as x .

A few experiments were made with alcohol vapour; this causes an effect of the same character as CHCl_3 and ether, but as it also causes an enormous increase in the resistance of the tissue, due to drying, the experiments were not proceeded with further.

When, in the second part of each experiment, the anæsthetic is applied to the other part of the nerve, the final result is similar to that of Series I, where the whole nerve is at once anæsthetised. As can be seen, there is a small residual E.M.F., occasionally (in other experiments not quoted here); this may reach a value of 0.005 to 0.006 volt, the exact significance of this is still uncertain.

Series IV.

In this series, CHCl_3 and ether vapours of different strength were applied simultaneously to both sides of the nerve. The result could have been predicted from an examination of Series I and II, but is a useful control, as certain sources of error are eliminated.

Experiment.	Central End.	Peripheral End.	E.M.F. initial.	E.M.F. final.
	per cent.	per cent.		
931	51.0 (ether)	16.1 (CHCl_3)	+ 33	— 1
932	16.1 (CHCl_3)	—	— 8	— 233
933	12.5 (CHCl_3)	16.5 (CHCl_3)	+ 13	— 18
934 { <i>a</i>	8.0 (CHCl_3)	} 14.5 (CHCl_3)	— 16	— 184 (<i>a</i>)
{ <i>b</i>	14.5 (CHCl_3)			— 16 (<i>b</i>)
113	54–32.5 (ether)	12.3 (CHCl_3)	— 25	— 7

If the small final values under 20 be disregarded, these experiments show that:—

(1) Ether vapour of 51 to 54 per cent. and CHCl_3 of 16 to 12·3 per cent. are identical in their final effects.

(2) CHCl_3 of 8 per cent. has a less effect. CHCl_3 vapour of about 12 per cent. has, therefore, a maximum action.

(3) Ether acts more quickly than CHCl_3 (fig. 5).

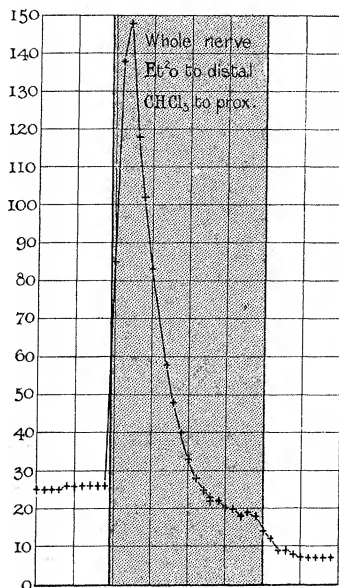


FIG. 5.—Series IV.

Control Experiments.

In order to exclude any possible source of current from electrodes or any unexpected physical cause, control experiments were made with threads moistened with (a) salt solution, (b) egg albumen, (c) egg yolk, and (d) fresh blood. These were treated in an exactly similar manner to the nerves in Series II. No electromotive phenomena followed the application of CHCl_3 vapour. So also nerves kept in salt solution until they gave no injury current showed no results with anæsthetic vapours. HCl and NH_4OH gave electromotive effects when applied either to threads or nerves, HCl with the same sign as CHCl_3 , NH_4OH with the reverse. The similarity is therefore only apparent and probably due to diffusion into the electrodes.

Series V.

The effect on the electrical resistance of the application of anæsthetic vapours is of great importance in endeavouring to give an explanation of the facts recorded above, and so, although the question has already been studied by Waller,* I have performed a considerable number of experiments in order to eliminate as far as possible the numerous sources of error present.

The method finally adopted was to place the nerve on non-polarisable electrodes in a chamber, pass in air saturated with water vapour, and take several successive readings until either they remained constant or else the rate of change was determined. Moist CHCl_3 vapour was then admitted for five minutes, a reading taken, the chamber washed out with moist air for four minutes, and the final value observed. A linen thread wet with M/10 NaCl solution rested on non-polarisable electrodes in the same chamber, and readings of its resistance were taken alternately with the nerve. A thermometer as close to the nerve and thread as possible gave an approximation to the temperature; as will be seen, the mean variation of this is about 0.4°C. , and in view of the difficulty of securing an equal amount of moisture and an equality of salt content in the electrodes, threads and nerves, the temperature error may for the present purpose be disregarded.

Two methods of determining the resistance were used :—

(1) The ordinary Wheatstone bridge, using non-polarisable electrodes and a constant current from one Leclanché cell.

(2) A slightly modified Kohlrausch apparatus, using the same electrodes and alternate currents.

With the control threads the results were identical; both sets of readings show a diminution of resistance of about 2 per cent. after CHCl_3 , in part due to temperature alterations, in part to other causes. The nerves on the other hand gave markedly different figures with the two methods.

* Waller, 'Proc. Physiol. Soc.,' November 12, 1898

Series V.
A.—Frog's Sciatic. Wheatstone Bridge.

Experiment.	Resistance before CHCl_3 (ohms) R_1 .	T° before.	Resistance during $R_2 \text{CHCl}_3$.	T° during.	Resistance after $\text{CHCl}_3 R_3$.	T°	Percentage of CHCl_3 vapour.	R_3/R_1 .	Notes.
168 A	107,300	$16^\circ 8$	107,800	$17^\circ 2$	106,200	$16^\circ 2$	14.5	0.990	Thread
B	142,100		150,700		121,700			0.858	Nerve
169 A	92,000	$16^\circ 9$	94,100	$17^\circ 3$	93,600	$17^\circ 0$	15.5	1.02	Thread
B	95,400		102,300		86,700			0.909	Nerve
170 A	110,000	$16^\circ 7$	108,000	$17^\circ 1$	105,600	$17^\circ 0$	17.0	0.960	Thread
B	117,700		107,400		90,700			0.770	Nerve
171 A	115,300	$16^\circ 3$	114,800	$16^\circ 5$	111,500	$16^\circ 6$	—	0.967	Thread
B	130,400		140,300		114,700			0.880	Nerve
Mean of 4 thread Experiments (A)	106,100	$16^\circ 68$	106,200	$17^\circ 03$	104,300		—	0.984	
Mean of 4 nerve Experiments (B)	121,400		125,200		103,500			0.852	

Series V—*continued.*

B.—Frog's Sciatic. Kohlrausch.

Experiment.	Resistance before CHCl_3 (ohms).	T. before.	Resistance during CHCl_3 .	T. during.	Resistance after CHCl_3 .	T. after.	Percentage of CHCl_3 vapour.	R_2/R_1 .	Notes.
201 A	125,000	17.0	125,000	18.0	122,000	16.5	—	0.976	Thread
B	82,000		88,000		85,000			1.036	Nerve
202 A	81,000	16.8	80,000	17.3	78,000	17.3	16.0	0.963	Thread
B	85,000		90,000		87,000			1.023	Nerve
203 A	88,000	17.6	90,000	18.3	92,000	18.0	16.0	1.045	Thread
B	80,000		82,000		79,000			0.987	Nerve
204 A	81,000	16.5	80,000	17.5	77,000	17.5	13.5	0.951	Thread
B	176,000		176,000		172,000			0.973	Nerve
205 A	111,000	17.5	110,000	17.8	107,000	17.8	13.0	0.964	Thread
B	190,000		199,000		183,000			0.963	Nerve
Mean of 5 thread Experiments (A)	97,200	17.08	97,000	17.78	95,200	17.42	—	0.979	
Mean of 5 nerve Experiments (B)	122,600		127,000		121,200			0.989	

These figures show that—

(1) Nerves tested by Wheatstone's bridge show an apparent diminution of resistance after CHCl_3 of about 15 per cent.

(2) Nerves tested by the Kohlrausch method show no alteration of resistance.

The difference between the two methods is that any polarisation in the nerve appears by the first as an added resistance. The figures in the first column of A therefore represent resistance and polarisation, and the conclusions follow—

A. CHCl_3 diminishes the polarisation of nerve;

B. CHCl_3 does not alter the real resistance of nerve within the limit of error of the method.

If the diminution in the control experiments is taken as a correction to be applied to the nerves, the resistance of these after CHCl_3 is increased by 1 per cent., at present it is doubtful if this correction is to be applied.

[*Note added December 12.*—A fresh series of experiments (Nos. 211 to 214) gave the final ratio for nerves slightly *less* than the control threads. The probable limit of error of the resistance experiments in the text is about ± 2 per cent., and as this lies in the object examined rather than in the measurements, greater accuracy seems at present unattainable.]

Series VI.

Similar experiments were made with ether, taking readings by both methods. The control threads now show a diminution of about 5 per cent. and an increase during etherisation. Except in this latter particular the nerves gave results almost identical with CHCl_3 .

Series VI.

Experiment.	Resistance before ether, ohms = R_1 .	T° .	Resistance during.	T° .	Resistance after, R_3 .	T° .	R_3/R_1 .	Percentage of ether.	Notes.
A ¹ .—Control Threads. Ether. Wheatstone Bridge.									
162	71,700	18.2	86,000	—	71,000	18.0	0.990	40.0	In this series the nerves and threads were measured successively, and the temperature was taken in the vapour of the ether, and not alongside the nerve as elsewhere
165	122,400	18.8	143,000	—	110,400	18.4	0.893	50.0	
167	105,200	18.7	127,000	—	100,900	18.5	0.959	52.4	
	99,770	—	118,600	—	94,100	—	0.947		
A ² .—Sciatic of Frog.									
161	156,600	17.9	169,300	1.0	129,300	17.9	0.826	55.0	
163	86,400	18.2	106,600	—	78,700	17.8	0.911	51.0	
164	165,800	19.0	190,000	—	141,300	18.8	0.852	47.2	
166	163,900	18.7	198,000	—	142,400	18.5	0.869	50.0	
	143,180		165,980	—	122,910	—	0.865		
B.—Frog's Sciatic and Thread. Kohlrausch. Ether at 50 per cent. approx.									
207 A	74,000	18.4	98,000	18.8	71,000	18.6	{ 0.960	—	Thread
B	68,000		109,000		73,000		{ 1.073	—	Nerve
208 A	90,000	18.5	118,000	18.6	83,000	18.5	{ 0.921	—	Thread
B	85,000		129,000		85,000		{ 1.000	—	Nerve
209 A	66,000	17.8	83,000	18.2	63,000	18.2	{ 0.955	—	Thread
B	72,000		103,000		69,000		{ 0.958	—	Nerve
210 A	103,000	18.2	132,000	18.5	99,000	18.3	{ 0.961	—	Thread
B	77,000		116,000		73,000		{ 0.959	—	Nerve
Mean of 4 thread (A)	83,300	18.2	107,800	18.5	79,000	18.4	0.949		
Mean of 4 nerves (B)	75,500	18.2	114,300	18.5	75,000	18.4	0.994		

These figures show—

- (1) Ether diminishes the polarisation in nerve.
- (2) Ether does not alter the real resistance of nerve (with the same reserve as to the control experiments).

Comparing the result of the two anæsthetics, and taking the mean figures :—

	Mean resistance before.	Mean resistance after.	R_2/R_1 .	
Nerve, CHCl_3	121,400	103,500	0·854	} Wheatstone.
„ ether	143,180	122,910	0·865	
Nerve, CHCl_3	122,600	121,200	0·989	} Kohlrausch.
„ ether	75,500	75,000	0·994	

The final effects of CHCl_3 and ether are identical, within the limits of error of the experiments.

Observations.

The full discussion of the problems raised by the facts here recorded must be deferred until the results are considered of experiments on other tissues and on the question as to the actual effect of the action of CHCl_3 and ether on proteid solutions.* Taken as they stand, the present experiments show :—

(1) That chloroform and ether (and probably alcohol) produce an electromotive effect when acting on a frog's nerve, which has a maximum value of about 0·030 volt, and the same sign as the current of injury.

(2) That CHCl_3 and ether produce no alteration of the resistance of the nerve (within the limits of error), but diminish the polarisation.

Two inferences present themselves—

A. That the electromotive effects are due to the same cause that produces the injury current.

B. That as the resistance is not diminished no additional ions are formed.

The discussion on the correctness or otherwise of these inferences is postponed for the reasons given.

I have again great pleasure in acknowledging the kindness of Dr. Waller, both for the permission to work in the laboratory of the University of London, and for advice in the conduct of the experiments. Also to express my appreciation of the assistance of Dr. B. J. Collingwood, in conjunction with whom many of the experiments were carried out. Mr. Shapiro has also given me much help in the later stages of the research.

* See Moore and Roaf, 'Roy. Soc. Proc.,' and also Waller, *loc. cit.*

APPENDIX. Protocols of Experiments in Series III.

The figures given are those of the potentiometer, balancing the current from the nerve at 30 sec. intervals.

CHCl ₃ .					Ether.
Experiment 107. Electrode current -3.	Experiment 108. Electrode current -6.	Experiment 109. Electrode current -8.	Experiment 110. Electrode current = +4.	Experiment 111. Electrode current -8.	Experiment 117. Electrode current -8.
-156 -154 -151 149 148 146 T° = 17°·3 145 145 143 -141	-184 -182 179 $\frac{1}{1000}$ = 2·7 177 175 174 172 171 169 168 -167	- 21 $\frac{1}{1000}$ = 3·3 - 21 21 22 no cut end 23 23 23 22 - 22 - 22	-176 $\frac{1}{1000}$ = 3·5 -175 -175 175 175 175 176 176 175 -175	- 25 - 26 26 27 27 no cut end 27 25 25 - 25	- 8 $\frac{1}{1000}$ = 2·0 - 9 10 11 11 no cut end 12 12 12 - 12
CHCl ₃ to long. surf. -120 - 80 - 45 - 20 + 8 + 25 35 44 52 58 63 66 68 70 71 72 72 73 73 + 74 T° = 17°·2 C. CHCl ₃ off	CHCl ₃ to long. surf. -144 -114 - 84 - 50 - 20 - 20 + 7 + 30 46 60 67 $\frac{1}{1000}$ = 3 div. 75 80 T° = 16°·8 85 88 92 94 95 96 97 + 99 CHCl ₃ off	CHCl ₃ to prox. end. + 20 + 50 + 78 + 94 105 118 130 130 132 142 146 150 148 150 153 155 158 158 +159 +160 CHCl ₃ off	CHCl ₃ to cut end. -190 -218 -233 254 254 268 280 290 296 302 304 306 307 308 308 307 306 306 306 -304 CHCl ₃ off	CHCl ₃ distal end. - 90 -120 160 189 210 210 227 238 243 247 247 249 250 252 252 257 255 255 255 255 254 -254 CHCl ₃ off	Ether to distal end. -120 -200 250 270 272 270 $\frac{1}{1000}$ = 1·6 269 267 267 -266 Ether off 5 mins. application only

- 24 24 24 24 23 23 21	- 17 17 17 17 17 17 17	- 27 29 28 28 27 26 25 23 25	- 32 32 31 31 30 30 26	- 14 11 10 9 9 7 8	- 6 6 6 8 9 9
CHCl ₃ to whole nerve. - 20 22 22 Electrode current = -3	CHCl ₃ to whole nerve. - 17 16 17 17 Electrode current = -4	CHCl ₃ to whole nerve. - 33 33 33 33 Electrode current = -9, 1000 = 2·8	CHCl ₃ to whole nerve. - 28 26 25 24 Electrode current = -11	CHCl ₃ to whole nerve. - 18 14 13 13 Electrode current -6	Electrode current = -11